RECENT STUDIES IN PRIMARY PULMONARY HYPERTENSION INCLUDING PHARMACODYNAMIC OBSERVATIONS ON PULMONARY VASCULAR RESISTANCE*

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PRIMARY pulmonary hypertension appears to be diagnosed more frequently. It is distinguished from secondary pulmonary hypertension by the absence of any intrinsic heart or lung disease and by the absence of mechanical blocks in the pulmonary vascular bed seeded from without, e.g., pulmonary emboli. Cardiac catheterization, of course, has given impetus to this by making possible the measurement of pulmonary vascular pressures as well as by ruling out certain congenital deformities. Wood,[1] in England, found six cases which he classified as idiopathic pulmonary hypertension during a study of 233 unselected cases of suspected congenital heart disease, 152 of which were catheterized. Chapman[2] in a similar study so diagnosed two of seventy-two patients who had right heart catheterizations. It seems that many people working in cardio-pulmonary laboratories have had the experience of studying some patients with pulmonary hypertension and failing to establish the etiology of the hypertension despite careful evaluation by recognized clinical and physiological methods. However, primary pulmonary hypertension should not be a "waste paper basket" category into which are tossed all the apparently unexplained diagnoses of pulmonary hypertension. The syndrome of primary pulmonary hypertension is fairly distinct. The diagnosis should be made not only by a process of elimination but by looking for and recognizing the definite clinical characteristics of this syndrome of which the patho-physiological processes can be evaluated in the cardio-pulmonary laboratory.

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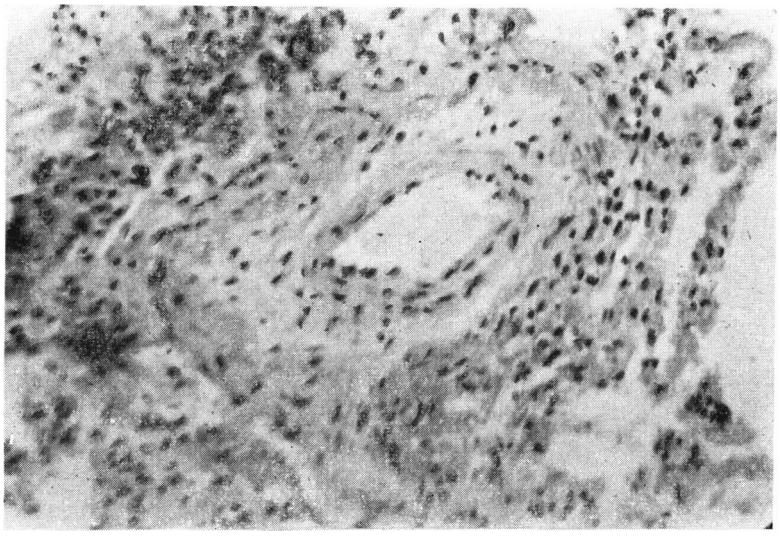

Fig.1—Marked intimal sclerosis of a small intrapulmonary artery is noted; X 500.
(See page 206 for permission to reproduce Figs. 1, 2, 4 and 5.)

Primary and secondary pulmonary hypertension are associated with right ventricular hypertrophy and also, in many instances, pulmonary vascular sclerosis. The etiology of pulmonary hypertension without any vascular changes as the cause of right ventricular hypertrophy had evoked much speculation prior to the cardiac catheterization era. De Navasquez and his associates[3] in 1940 preferred to designate their three autopsied cases with right ventricular hypertrophy and without abnormal pulmonary vascular changes as "idiopathic right ventricular hypertrophy" rather than introduce the concept of pulmonary hypertension. Soothill[4] in 1951 reported a case of primary pulmonary hypertension in a twenty-two year old male whose pulmonary artery pressure was 128/83 mm. Hg. At necropsy, the heart and lungs were sent to Dr. De Navasquez. The note that Dr. De Navasquez sent back describing the organs included the following statement: "The heart and lungs appeared to show the abnormalities usually associated with most cases of idiopathic right ventricular hypertrophy without any additional features."

All cases of primary pulmonary hypertension show marked right ventricular hypertrophy but the pulmonary vascular changes have not always been present. That pulmonary vascular changes may accompany

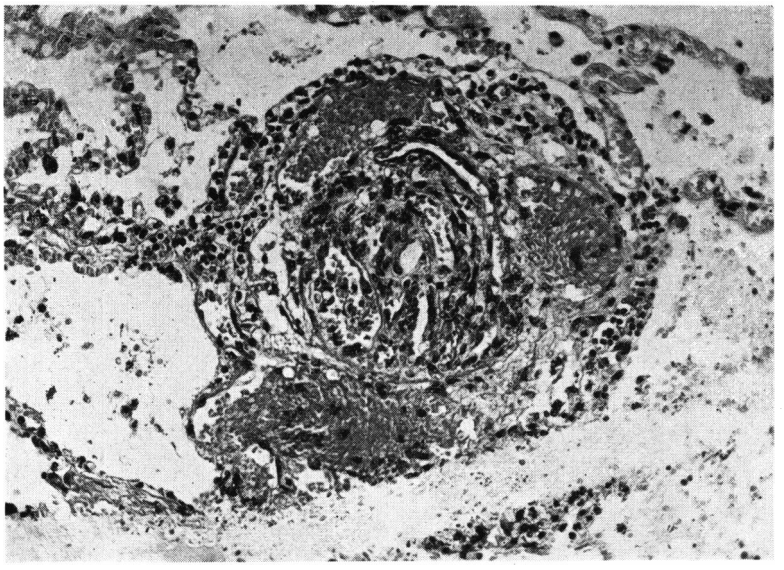

Fig. 2—A recanalized thrombus in a pulmonary vessel of microscopic size is seen; X 250.

prolonged pulmonary hypertension, not unlike the vascular changes seen in systemic hypertension, can be appreciated more readily by the following papers entitled: Primary Pulmonary Arteriosclerosis with Hypertrophy of the Right Ventricle,[5] Primary Pulmonary Vascular Sclerosis,[6,7] Obliterative Pulmonary Arteriolosclerosis,[8] and so forth, which report autopsied cases that we feel fall into the category of primary pulmonary hypertension. The pulmonary vascular changes that occur are found proximal to the capillaries. When present, they have shown considerable variation in their nature, distribution, and severity. The predominant changes are atheromatous lesions of the stem and large elastic arteries, alone, or in conjunction with fibrous intimal thickening and narrowing (Fig. 1), or obliteration of the smaller arteries. Occasionally, medial hypertrophy has been described. Thrombotic lesions in various stages of organization have been seen in the precapillary and postcapillary vessels of microscopic sizes (Fig. 2).[9] When present, these lesions are seen much less frequently than the sclerotic changes. It is interesting that Rich[10] described similar thrombotic lesions in 90 per cent of the cases of tetralogy of Fallot that he studied. Lesions of a

similar nature have also been described in the pulmonary vessels of long-standing mitral stenosis with pulmonary hypertension.[11, 12] Dr. Rich felt that the lesions he described were due to the sluggish pulmonary blood flow and to the polycythemia. Decreased pulmonary blood flow is found in patients with pulmonary hypertension, either of the primary type,[4, 9] or secondary to mitral stenosis.[13-16] Thrombotic lesions, as mentioned before, coexist with extensive pulmonary vascular sclerosis. It is suggested, therefore, that these thrombotic lesions may be a result of the markedly narrowed vessels and the sluggish pulmonary blood flow.

Primary pulmonary hypertension is not limited to any age group, having been described in patients as young as twenty months[7] and found in the eighth decade.[8] The majority of cases, however, fall in the age group of twenty to forty years. There appears to be a slightly greater incidence in the female sex. That a familial tendency might exist is suggested by studies made possible through the courtesy of Dr. E. P. Maynard and Dr. W. Dressler on a mother, her sister, and her son. All had the criteria for the diagnosis of primary pulmonary hypertension. A brother of the mother is reported to have died of an undiagnosed heart disease at an early age. The mother died at the age of forty-three, the sister died at thirty-one, and the son died at twenty-one, all in severe right heart failure.

Congenital defects were ruled out in both the mother and son by right heart catheterization. Pulmonary function studies on the son were all within the normal range. His pulmonary artery pressure was 78/33 mm. Hg, his systemic pressure was 97/56 mm. Hg and his arterial oxygen saturation was 95 per cent. It was not possible to do pulmonary function studies on the mother. Her pulmonary artery pressure was 122/52 mm. Hg and at the same time her systemic pressure was 110/68 mm. Hg. Her blood oxygen saturation was 92 per cent at a time when she was deeply sedated. The sister's diagnosis was based solely on the clinical findings, as well as electrocardiographic and x-ray studies. Electrocardiographic changes in this syndrome are those consistent with right ventricular hypertrophy.

Primary pulmonary hypertension runs a malignant course characterized by right heart failure, not infrequently terminating in sudden death. The salient clinical features in order of their frequency are listed. 1) Exertional dyspnea and weakness, probably related to the decreasing cardiac output, are the most prominent symptoms and are present in all

the patients. 2) Exertional substernal and left chest pain, resembling angina, is present in approximately 25 per cent of the patients. This symptom has also been described by Viar and his associates[17] as occurring in some patients with secondary pulmonary hypertension. They felt that the most likely cause for the pain was the distention of the pulmonary artery. We had proposed in a former communication[9] on this subject that it might be due to a combination of severe right heart failure resulting secondarily in diminished left heart output and decreased coronary blood flow. The decrease in cardiac output on exertion is also associated with a marked increase in the right ventricular end-diastolic pressure, thus causing increased resistance to coronary flow in the right ventricle during diastole. No associated coronary artery disease has been described in these patients at necropsy. 3) Exertional syncope occurs in about 20 per cent of the patients and, when present, is of diagnostic importance. Dressler[18] felt that this might be related to a vasovagal state, the impulses arising from the pulmonary vascular bed. It was our impression that syncope, as well as angina, was related to acute right heart insufficiency. In one of our patients mounting precordial distress immediately preceded the syncope. Acute right heart failure as a cause of syncope was suggested independently recently by Dr. Howarth[19] in England. 4) Palpitation or awareness of heart beat is reported but is probably not related to auricular fibrillation since this has been a rare finding except terminally. 5) Rarely, orthopnea has been described[6] as a terminal feature. This was not seen in our cases. 6) Hemoptysis has been described[6] in a few instances with no evidence of pulmonary infarction at necropsy. The mechanism for the hemoptysis, a rare finding, is not clear.

Positive physical findings are usually limited to the heart and organs affected later by an elevated venous pressure. Protracted distention of the neck veins and hepatomegaly are frequently observed unassociated with peripheral edema which appears later. Examination of the heart reveals evidence of marked right ventricular hypertrophy as characterized by the increased retrosternal dullness, widening of the conus area and a distinct pulsating bulge of the precordium, most marked along the left margin of the sternum.[20] The second pulmonary sound is markedly accentuated. Systolic murmurs may be present over the precordium due to relative tricuspid insufficiency, and over the pulmonic area due to the dilated pulmonary artery. Diastolic murmurs at the pul-

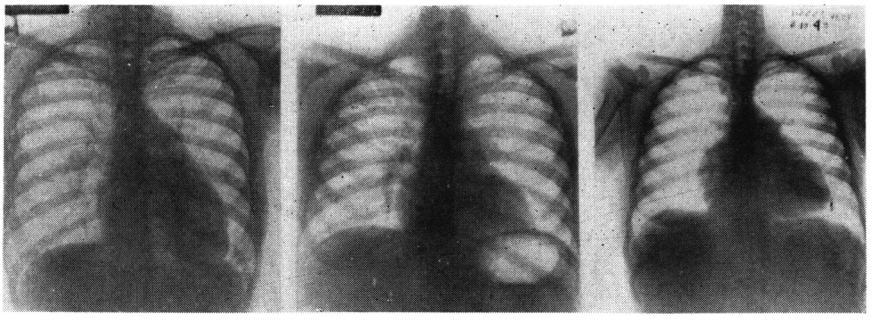

Fig. 3—Chest x-rays of three members of the same family showing prominent pulmonary artery segments, prominent hilar vessels and normal or decreased pulmonary vascular markings.

monic area and left sternal border may be present because of a functional pulmonary valvular insufficiency. Various degrees of cyanosis without clubbing of the fingers may be seen. All our patients, except the one in whom there was a complicating patent foramen ovale, were not cyanotic until very late in the disease. Anoxia due to decreased blood flow could explain the late appearance of cyanosis since our patients showed normal oxygen saturations and decreased cardiac output with increased arteriovenous oxygen difference. The mechanism of cyanosis in primary pulmonary hypertension with patent foramen ovale is similar to that in pulmonic stenosis with patent foramen ovale.

Routine laboratory studies are normal except for an occasional report of mild polycythemia. Pulmonary function studies utilizing the techniques reported by Baldwin and her associates[21] are within normal limits. Hemodynamic studies at rest utilizing the technique of right heart catheterization show the following: 1) Markedly elevated pulmonary artery pressure, 2) normal systemic artery pressure, 3) low cardiac output, 4) increased arteriovenous oxygen difference, 5) elevated right ventricular end-diastolic pressure, sometimes present before clinical signs of right heart failure, and 6) normal arterial oxygen saturation (unless complicated by patent foramen ovale).

The x-rays (Fig. 3) of the family previously mentioned are typical of those seen in primary pulmonary hypertension. The characteristic findings as demonstrated by these x-rays are: 1) Right ventricular hypertrophy, 2) bulging pulmonary artery segment, 3) prominent hilar ves-

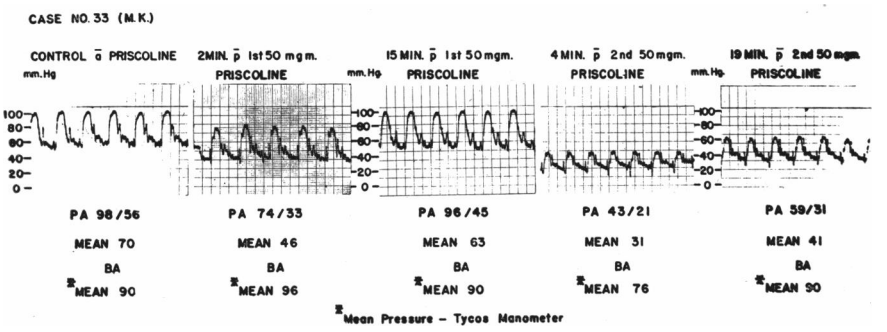

Fig. 4—There is a striking fall in the pulmonary artery pressure after parenteral Priscoline, most marked after the second dose, which was administered 18 minutes after the first dose.

sels, and 4) normal or decreased intrapulmonary vascular markings. No evidence of left atrial enlargement is found. Overlapping of the spine by the cardiac silhouette in the left anterior oblique view may occur without left ventricular enlargement in the presence of marked right ventricular hypertrophy.[9]

The beneficial effects of Priscoline®, a sympatholytic and adrenolytic agent, on the pulmonary vascular resistance in the acute study in patients with primary pulmonary hypertension has been reported previously.[9] Figures 4 and 5 taken from our earlier report illustrate this. There is a striking fall in the pulmonary artery pressure following the parenteral administration of Priscoline®. This occurred while there was a marked increase in the blood flow and symptomatic improvement in the patient. This patient, who could not do more than 16 step-ups on the platform used in our pulmonary function studies because of precordial distress and weakness, was able to do over 70 step-ups without symptoms following the intravenous administration of 75 mg. of Priscoline®. It can be seen that Priscoline® affected the pulmonary vascular resistance more than the systemic resistance. On the other hand, tetraethylammonium chloride had its greatest effect on the systemic vascular resistance. Although all the patients studied with primary pulmonary hypertension did not show the same striking fall in pulmonary arterial pressure, they all showed a significant increase in cardiac output and a significant decrease in the calculated pulmonary vascular resistance. These results suggest that the pulmonary vascular resistance in part, at

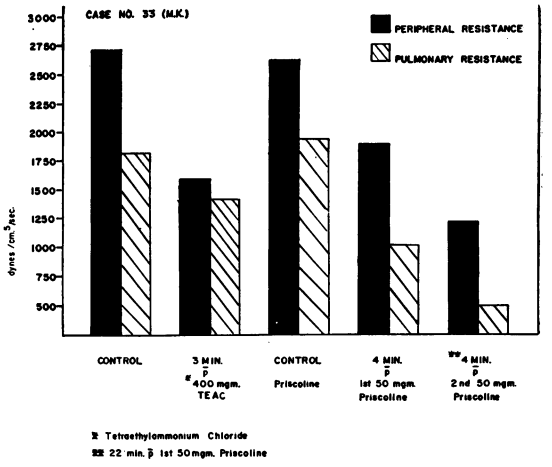

Fig. 5—The predominant effect of TEAC was on the peripheral resistance whereas Priscoline exerted its maximal effect on the pulmonary resistance.

least, can be modified. Furthermore, the absence of pulmonary vascular changes at necropsy in patients whose pulmonary artery pressure was found elevated during life,[4,22,23] as well as our Priscoline® studies suggest that the cause for the increased vascular resistance in some instances was due to increased vascular tone and not due to organic changes. That the stimulus for this increased vascular resistance is not due to anoxia is indicated by the normal arterial oxygen saturation found in the uncomplicated case and the absence of intrinsic pulmonary disease. In addition, the pulmonary hypertension would not seem to be due to increased pulmonary blood volume since there is decreased intrapulmonary vascularity by x-ray. There was a normal total blood volume in two of three patients in whom this was measured.[9]

It is proposed that the increased vascular tone is present in the precapillary vascular bed. It has been postulated that the increased pulmonary vascular tone in some instances occurs beyond the pulmonary arterioles.[23,24] If that were so with primary pulmonary hypertension, it would mean that the pulmonary capillary bed in those individuals would have been subjected to extremely high pressures. It has been demonstrated by Gorlin[15] that when the pulmonary capillary pressure reaches a level of 30 mm. Hg or higher for a period of time, clinical evidence of pulmonary edema can be found. Our own unpublished observations

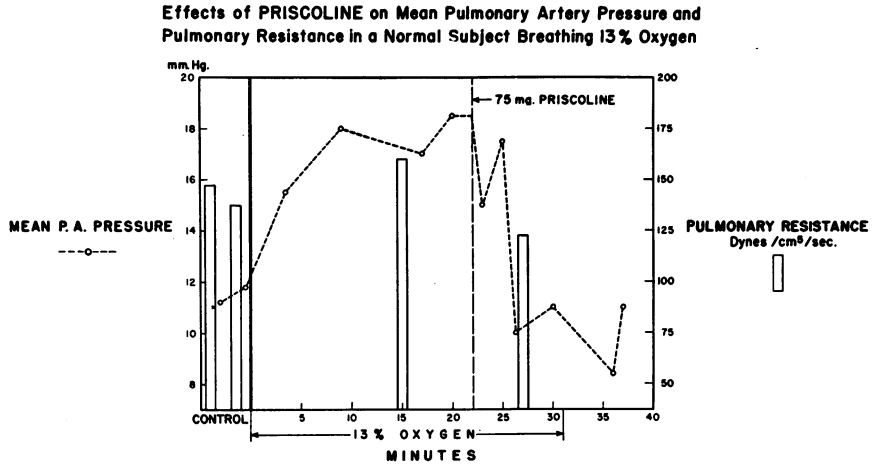

Fig. 6—Priscoline causes a marked drop in the pulmonary artery mean pressure and pulmonary resistance which was elevated by 13 per cent oxygen breathing.

support this. Our patients with primary pulmonary hypertension had pulmonary artery mean pressures greatly in excess of the critical capillary pressures. Clinically and roentgenologically they did not show any evidence of pulmonary edema. Furthermore, capillary changes, such as seen in long-standing mitral stenosis with pulmonary hypertension, have not been demonstrated at necropsy.

Further studies are indicated to determine what may be the stimulus in these patients to bring about the demonstrated increased pulmonary vascular resistance. The Priscoline® studies would suggest either an overactivity of the sympathetic nervous system or a local effect on the pulmonary vascular bed. A ganglionic blocking agent, tetraethylammonium chloride, was demonstrated not to have as marked effect on the pulmonary vascular resistance as Priscoline®. Griswold and his associates[25] reported two cases of idiopathic pulmonary hypertension in children. In one, a thoracic sympathectomy involving the ganglia from T_2 to T_6 and a hilar plexectomy were performed. The immediate results indicated that this patient was not benefited by this procedure. Lung biopsies performed at the time of operation did not show any abnormal pulmonary vascular changes.

Further studies have been conducted in our laboratory in an attempt to elucidate some of the mechanisms involved in controlling the pul-

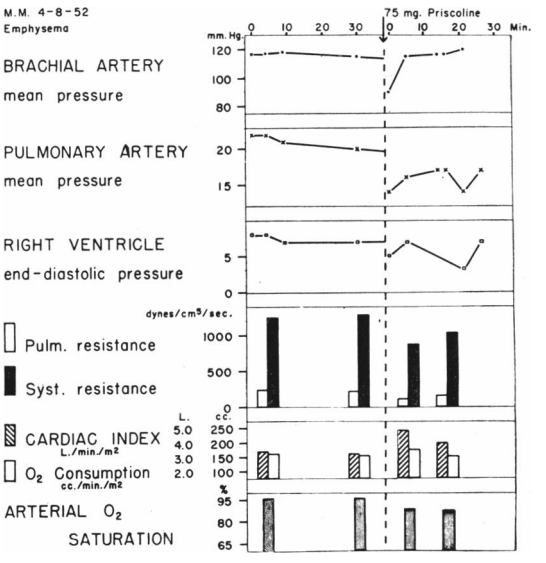

Fig. 7—There is a sustained fall in the pulmonary artery pressure with an increase in cardiac output following Priscoline. Note the drop in arterial oxygen saturation at the same time.

monary vascular tone. Since it was shown that Priscoline® had an effect upon the pulmonary vascular bed in primary pulmonary hypertension we were curious as to its effect on pulmonary hypertension induced by anoxia in normal man and its effect on the pulmonary hypertension found secondary to pulmonary disease.[26]

Our studies suggest that stimuli for increasing the pulmonary vascular resistance in primary pulmonary hypertension, in acute anoxia, and in the cor pulmonale syndrome are mediated through a mechanism that can be acted upon by Priscoline®. The effects of Priscoline® upon the pulmonary artery pressure and calculated pulmonary vascular resistance in a normal male after breathing 13 per cent oxygen for twenty-two minutes are illustrated in Fig. 6. The arterial oxygen saturation rose from 75 per cent before Priscoline® and 13 per cent oxygen breathing to 80 per cent after Priscoline® and 13 per cent oxygen breathing. Figure 7 illustrates some of the hemodynamic changes that occurred in a patient with moderately severe emphysema before and after the administration of Priscoline®. Concomitantly with the drop in pulmonary vascular re-

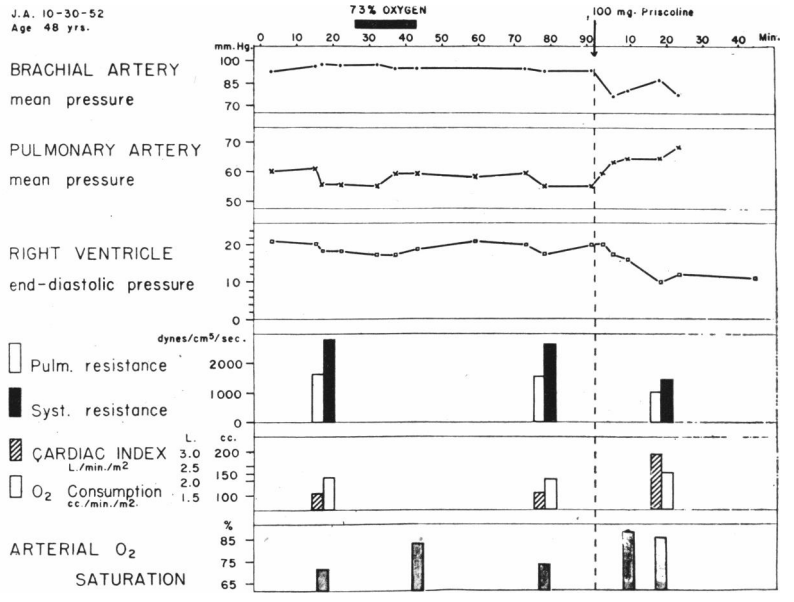

Fig. 8—There is a fall in right ventricular end-diastolic pressure, an increase in cardiac output, decrease in pulmonary vascular resistance and a rise in arterial oxygen saturation following Priscoline.

sistance after Priscoline® the arterial oxygen saturation fell from 96 per cent to 87 per cent. This suggests that poorly ventilated areas in the lungs that were not perfused during the control period became perfused following Priscoline®.

In view of the beneficial effects of Priscoline® in patients with primary pulmonary hypertension in the study of short duration, it was felt that it could be used in the diagnostic armamentarium in patients with suspected primary pulmonary hypertension complicated by patent foramen ovale by possibly neutralizing the interatrial shunt.[27] The effects of Priscoline® in such a patient are illustrated in Fig 8. The blood flow increased concomitantly with a decrease in pulmonary vascular resistance similar to that seen in the patient with pulmonary emphysema with the exception of the effects on the arterial oxygen saturation which rose from 71 per cent in the control period to 88 per cent after Priscoline®. The increased arterial oxygen saturation after Priscoline®, higher than when the patient breathed 73 per cent oxygen, occurred concomitantly with increased blood flow to the left atrium and a drop in right ventri-

cular end-diastolic pressure. The latter would cause a drop in right atrial mean pressure. These data could be interpreted as demonstrating the mechanisms in neutralizing the right to left interatrial shunt. The diagnosis of primary pulmonary hypertension with patent foramen ovale was confirmed by autopsy on this patient.

Patients with the Eisenmenger complex and severe precapillary pulmonary vascular changes, or those with interatrial septal defect with precapillary pulmonary vascular changes and right heart failure, could present a clinical picture similar to patients with primary pulmonary hypertension and patent foramen ovale. The hemodynamics with Priscoline® in those patients could also be similar.

In summary, the salient clinical and hemodynamic features of the syndrome of primary pulmonary hypertension are presented. It is noted that pulmonary vascular changes are not always present. When pulmonary vascular changes are found they are on the arterial side and do not involve the capillaries.

Evidence is presented to show that the mechanisms for causing increased pulmonary vascular tone in primary pulmonary hypertension, in pulmonary hypertension induced by anoxia in normal man, and in the cor pulmonale syndrome are acted upon by Priscoline®. Data showing the neutralization of a right to left interatrial shunt in a patient with primary pulmonary hypertension and patent foramen ovale are presented.

Acknowledgement: Figures 1, 2, 4 and 5 are reproduced with permission of the *American Journal of Medicine.*

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